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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,568	05/02/2002	Dan L. Eaton	P3230R1C48	9762

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,568	EATON ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment received 09 September 2005 has been entered in full. Claims 1-5 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner Elizabeth C. Kemmerer, Ph.D.

35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to antibodies that bind the polypeptide of SEQ ID NO: 60, referred to in the specification as PRO1291 or DNA19610-1556. The utility of the antibodies The specification does not disclose any secondary or tertiary structural features of this polypeptide, nor does it assert that the polypeptide has any homology

with known, characterized polypeptides. The instant specification does not disclose any additional information regarding PRO1291 such as subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1291, and what physiological significance PRO1291 plays. Therefore, it is a totally new, uncharacterized polypeptide, and neither it, nor the antibody that binds it, has a well-established utility.

The specification discloses that PRO1291 tested positive in a microarray analysis wherein higher levels of cDNA clones corresponding to PRO1291 were detected in: 1) esophageal tumor versus normal esophagus; 2) lung tumor versus normal lung; and 3) normal skin versus melanoma tumor (Example 16, pp. 140+). However, this information does not provide a credible, specific and substantial utility for PRO1291 polypeptides or antibodies. While the data indicate that PRO1291 mRNA can reasonably be predicted to be elevated in: 1) esophageal tumor versus normal esophagus; 2) lung tumor versus normal lung; and 3) normal skin versus melanoma tumor, the data do no indicate that PRO1291 polypeptides would also be similarly elevated in these tissues. Specifically, the literature indicates a lack of correlation between mRNA levels and polypeptide levels. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein

expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that mRNA (transcript) levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-

1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal

and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Thus, the proposed use of the PRO1291 antibodies as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's arguments (pp. 3-9, amendment received 09 September 2005) have been fully considered but are not found to be persuasive for the following reasons.

From pp. 3 to 4, Applicant reviews the legal standard for utility and enablement rejections, with which the examiner takes no issue.

At p. 4, Applicant reviews the data disclosed in example 18 of the specification, asserting that the mRNA data supports the utility of the polypeptide and antibody. At p. 5, Applicant argues that the examiner is applying the wrong legal standard to support the rejection. Specifically, Applicant argues that the examiner has required Applicant to demonstrate that there is always a correlation between mRNA levels and polypeptide levels. Applicant urges that the proper legal standard for a *prima facie* rejection is a showing that it is more likely than not that there is not a correlation. Applicant argues that the rejection falls short of this standard. This has been fully considered but is not found to be persuasive. In view of the new evidence discussed above, it is submitted that the art shows that it is more likely than not that mRNA levels fail to predict trends in polypeptide levels. For example, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient

for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) teach that, for the most part, the literature has reported only minimal and/or limited correlations between mRNA and polypeptide levels in diseased and healthy tissues. See also Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., and Fessler et al.

At p. 6, Applicant argues that there may be specific instances wherein there is no correlation between mRNA levels and polypeptide levels; however, it is more likely than not that there is a correlation. Applicant argues that the scientific research community recognizes a strong general correlation between the amount of mRNA in a particular cell type and the amount of polypeptide expressed from that mRNA for any particular gene of interest. Applicant notes that Affymetrix experienced financial success in selling gene chip arrays for the purpose of measuring the amount of gene expression in a sample. Applicant reasons that the sale of these chips would not have been so prevalent in the biotechnology industry if the mRNA levels were not predictive of the level of polypeptide expressed from the mRNA. This has been fully considered but is not found to be persuasive. Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., LaBaer, and Greenbaum et al. constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. Regarding gene chips, it is submitted that evidence of financial success is not relevant to utility or enablement. Also, the chips may be purchased by a researcher for providing useful

information about genes, but not polypeptides. Finally, products that provide only potential or preliminary results may also sell well in the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels.

At p. 7, Applicant refers to the declaration of Dr. Polakis submitted under 37 C.F.R. § 1.132 with the response filed 09 September 2005. Applicant characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant quotes from the declaration wherein Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Applicant concludes that all of the submitted evidence supports Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence

or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not increased mRNA levels are predictive of increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) There is strong opposing evidence showing that, more likely than not, increased mRNA levels are not predictive of increased polypeptide levels. See, e.g., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors or melanoma tumors or esophageal tumors? How highly overexpressed were the mRNAs that correlated with increased polypeptide levels?

From p. 7 to p. 8, Applicant refers to Lockhart et al. (2000, Nature 405:827-836). Applicant characterizes the reference as providing evidence that microarrays are among the most powerful and versatile tools for genomics. Applicant ponders why microarrays would be characterized as such if there were no generally accepted correlation between mRNA and protein levels. Applicant quotes from Lockhart et al. at p. 830 wherein the

authors state that mRNA levels are immensely informative about cell state and activity of genes, and for most genes, changes in mRNA abundance are related to changes in protein abundance. This has been fully considered but is not found to be persuasive. As stated above, microarray chips may be purchased by a researcher for providing useful information about genes, but not polypeptides. The genes may urn out to be important diagnostic tools for diagnosis of disease. However, products that provide only potential or preliminary results may also be considered important to the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels. Most importantly, Lockhart et al. do not support their assertion that "for most genes, changes in mRNA abundance are related to changes in protein abundance" with reference to any facts or evidence. It is noted that Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al. all refer to facts in their conclusions that there is no general correlation between increased mRNA levels and increased protein levels. Finally, it is noted that Lockhart et al. also point out that, because of its importance, many methods have been developed for monitoring protein levels directly or indirectly (p. 830).

Applicant concludes that the evidence indicates that it is more likely than not that increased mRNA levels are predictive of increased polypeptide levels. Therefore, Applicant reasons that the specification's disclosure of differences in PRO1291 mRNA levels between tumor and healthy tissue indicates that it is more likely than not that PRO1291 polypeptide is also differentially expressed in the same tissues. Applicant

concludes that the PRO1291 polypeptide and antibodies can be used diagnostically and as therapeutic targets. This has been fully considered but is not found to be persuasive. As set forth above, the specification does not provide data that PRO1291 polypeptide is differentially expressed in any diseased tissues. The specification's data concerning differential expression of PRO1291 mRNA in diseased tissues is not predictive (more likely than not) based on the evidence in the art that mRNA levels are not predictive of protein levels in general. See Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al. In view of the preponderance of all of the evidence, the utility and enablement rejections are proper.

Conclusion

No claims are allowed.

In view of the newly re-instated utility rejection, this action is NOT made final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (571) 272-0829. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER